

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION

INTERNATIONAL APPLICATION PUBLISHING CENTER



WO 9603357A1

(51) International Patent Classification 6:

C07B 39/00, C07C 17/093

(43) International Publication Date: 8 February 1996 (08.02.96)

(21) International Application Number: PCT/GB95/01765

(22) International Filing Date: 26 July 1995 (26.07.95)

(30) Priority Data:  
9414974.7 26 July 1994 (26.07.94) GB

(71) Applicant (for all designated States except US): BNFL FLUOROCHEMICALS LTD. [GB/GB]; Springfields Works, Salwick, Preston PR4 0XJ (GB).

(72) Inventors; and  
(73) Inventors/Applicants (for US only): CHAMBERS, Richard, Dickinson [GB/GB]; University of Durham, Science Laboratories, South Road, Durham DH1 3LE (GB). SANDFORD, Graham [GB/GB]; University of Durham, Science Laboratories, South Road, Durham DH1 3LE (GB).

(74) Agent: McCORMACK, Derek, James; British Nuclear Fuels plc, Risley, Warrington, Cheshire WA3 6AS (GB).

(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published

With international search report.

(54) Title: SELECTIVELY FLUORINATED ORGANIC COMPOUNDS

(57) Abstract

A process for the preparation of a selectively fluorinated organic compound, which process includes reaction of a precursor of said organic compound, the precursor containing at least one Group VI element selected from sulfur, selenium and tellurium, with a fluorinating agent and another halogenating agent and characterised in that the fluorinating agent is elemental fluorine.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
RJ	Burma	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KR	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LJ	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Lithuania	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

Selectively fluorinated organic compounds

The present invention relates to selectively fluorinated organic compounds and their preparation.

The selective fluorination of organic molecules has received considerable attention because of the profound effect that fluorine can have on the physical, chemical and biological properties of a wide range of substrates. For example, the introduction of a difluoromethylene unit into a molecule is an important target since the  $\text{CF}_2$  group is isopolar and isosteric with an ether oxygen and has a steric profile not dramatically different to that of a methylene group. Consequently, effective methods for constructing fluorine containing groups such as fluoromethyl, difluoromethylene or trifluoromethyl from readily available, cheap fluorinating agents are highly desirable and many reagents have been developed in order to meet these targets.

The fluorination of sulfur containing substrates offers an attractive route to fluoromethyl, difluoromethylene or trifluoromethyl containing substrates as many sulfur containing organic compounds are readily available from inexpensive starting materials by well established chemistry. Several methods for the fluorodesulfurization of organic compounds have been devised.

These reactions are generally performed by reacting the appropriate sulfur containing substrate with a combination of a source of electrophilic halogen such as N-bromosuccinimide with a fluoride ion donor such as pyridinium poly(hydrogen fluoride). Thus, fluoromethyl containing substrates may be prepared by treating a phenyl thioglycoside with diethylaminosulfur trifluoride and N-bromosuccinimide. Difluoromethylene containing substrates may be prepared by reacting a 1,3-dithiolane with N-bromosuccinimide and pyridinium poly(hydrogen fluoride) or upon reaction with difluoroiodobenzene. Trifluoromethyl

containing substrates may be prepared by treating an orthothio ester with N-bromosuccinimide and pyridinium poly(hydrogen fluoride). However, many of these reagents suffer from the disadvantages of being difficult to handle, they may be highly toxic and may be expensive.

The fluorination of thiocarbonyl containing substrates offers an attractive route to gem-difluoromethylene compounds as such substrates can readily be prepared from aldehydes or ketones by well established routes.

Only a few methods for the fluorodesulfurization of thiocarbonyl containing substrates are known. These typically involve the synthesis of  $\alpha,\alpha$ -difluoroethers from thioesters upon reaction with diethylaminosulfur trifluoride (DAST) or with bromine trifluoride. No extension of these methods to other thiocarbonyl derivatives has been proposed and, in addition, the reagents used are toxic, are difficult to handle and may be expensive.

According to the present invention there is provided a process for the preparation of a selectively fluorinated organic compound, which process includes the reaction of a precursor of the said organic compound, the precursor containing at least one group VI element selected from sulfur, selenium and tellurium, with a fluorinating agent and another halogenating agent and characterised in that the fluorinating agent is elemental fluorine.

The group VI containing precursor may be a thiocarbonyl containing substrate.

The group VI containing precursor may be contained in an inert solvent.

Preferably, the inert solvent may be a neutral substance such as acetonitrile and desirably may be a polar solvent such as dichloromethane or chloroform or an acid such as sulfuric acid or trifluoroacetic acid.

The halogenating agent may comprise elemental iodine or bromine or an interhalogen compound. The interhalogen

compound may comprise iodine monochloride or iodine monobromide.

The process according to the present invention may be carried out by passing fluorine gas into the group VI containing precursor in solution in a suitable vessel. Alternatively, a flowing stream of the solution may be contacted with a gaseous flow of fluorine in countercurrent fashion.

The reaction of the process may be carried out at a temperature in the range -60°C to +150°C although a temperature of from -20°C to +50°C is preferred.

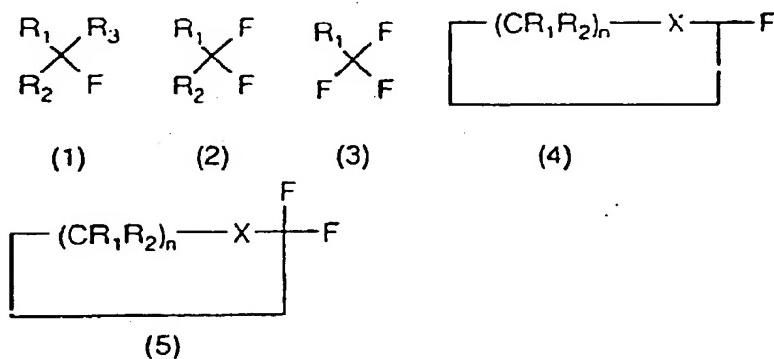
Preferably, the fluorine gas is diluted before use by mixing with an inert gas such as nitrogen or helium. The concentration of fluorine in the inert gas may be from 1% to 50% by volume, preferably from 2% to 25% by volume, and especially from 5% to 15% by volume.

When the fluorination reaction of the process is complete, the selectively fluorinated organic compounds may be isolated by purging the reaction mixture with an inert gas to remove any residual fluorine gas or hydrogen fluoride formed during the reaction, followed by dilution with an excess of aqueous sodium metabisulphite solution and extraction of the selectively fluorinated organic compounds into a suitable solvent followed by purification by distillation or column chromatography.

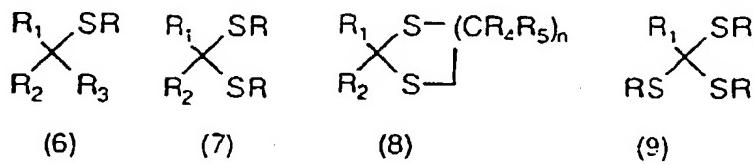
Surprisingly and beneficially the inventors have found that elemental fluorine can be used to convert sulfur containing substrates into corresponding fluoro, difluoro, or trifluoro compounds by relatively simple route using readily available, inexpensive starting materials. In addition, elemental fluorine, when used in conjunction with a halogen such as iodine, permits the difluorination of a wide range of thiocarbonyl derivatives at room temperature in common organic solvents by a process which does not suffer from any of the disadvantages of the methods previously applied to the difluorination of

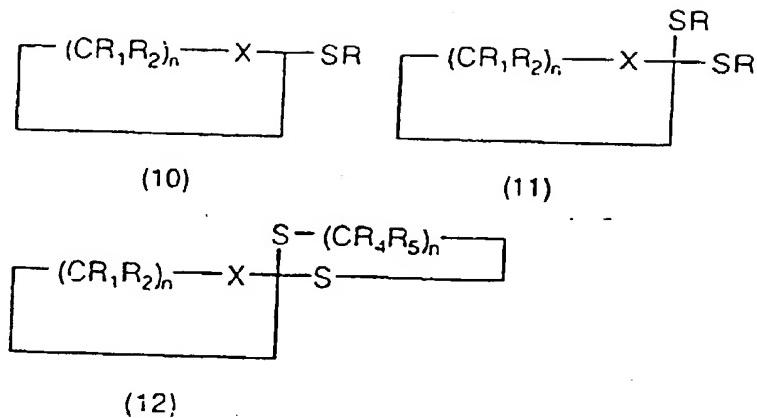
thiocarbonyls. The use of elemental fluorine for the site specific fluorination of organic compounds is rarely satisfactory due to the high reactivity of the element which may cause side reactions. However, in the case of the present invention, the reaction required can be controlled by selection of the rate of fluorine gas applied to the reaction.

The process of the present invention may be used to convert a wide range of compounds containing group VI elements, especially sulfur, to the corresponding fluorinated analogues. In particular, the preparation of fluorine containing compounds of formulae (1), (2), (3), (4) or (5) as follows:



comprises converting the corresponding precursor compounds of formulae (6), (7), (8), (9), (10), (11) or (12) as follows:





into the compounds (1), (2), (3), (4) or (5) by reaction with elemental fluorine as described hereinbefore.

The groups  $R_1$ ,  $R_2$  and  $R_3$  may be selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, aryl, substituted aryl, or acetoxy. Where any of the groups  $R_1$ ,  $R_2$  or  $R_3$  is an alkyl, cycloalkyl, or aryl substituent, the said group may include one or more optional substituents or hetero atoms.

The groups  $R$ ,  $R_4$ , and  $R_5$  may be selected from hydrogen, alkyl, cycloalkyl, aryl or substituted aryl.

The substituent  $X$  may include oxygen,  $NH$ ,  $NR$  or sulfur.

The structures represented by formulae (4), (5), (8), (10), (11) and (12) are cyclic and  $n$  may be an integer in the inclusive range from 1 to 8.

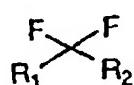
In carrying out the reaction, the ratio of fluorine to compound of formula (6) or (10) may be varied within wide limits although it is preferred that the molar ratio is in

the range 0.5 to 2.0:1, especially 1.1 to 1.25:1 (fluorine: organic compound). The ratio of fluorine to compound of formula (7), (8), (11) or (12) may be varied within wide limits although it is preferred that the molar ratio is in the range 1.5 to 2.5:1, especially 2.0 to 2.25:1 (fluorine: organic compound). The ratio of fluorine to compound of formula (9) may be varied within wide limits although it is preferred that the molar ratio is in the range 2.5 to 3.5:1, especially 3.1 to 3.25:1 (fluorine: organic compound).

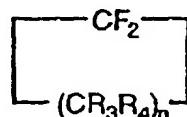
The ratio of halogen or interhalogen to compound of formula (6) or (10) may be varied within wide limits although it is preferred that the molar ratio is in the range 0.5 to 2.0:1, especially 1.1 to 1.25:1 (halogen/interhalogen: organic compound). The ratio of halogen or interhalogen to compound of formula (7), (8), (11), or (12) may be varied within wide limits although it is preferred that the molar ratio is in the range 1.5 to 2.5:1, especially 2.0 to 2.25:1 (halogen/interhalogen: organic compound). The ratio of halogen or interhalogen to compound of formula (9) may be varied within wide limits although it is preferred that the molar ratio is in the range 2.5 to 3.5:1, especially 3.1 to 3.25:1 (halogen/interhalogen: organic compound).

The process according to the present invention therefore provides an inexpensive and convenient synthetic route to fluorine containing organic compounds.

The process of the present invention may also be used to convert a wide range of thiocarbonyl compounds to the corresponding difluorinated analogues. In particular, the preparation of difluorinated compounds of formulae (13) or (14) as follows:

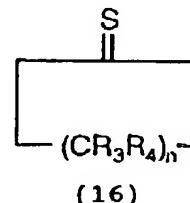
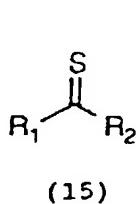


(13)



(14)

comprises converting the corresponding thiocarbonyl compounds of formulae (15) or (16) as follows:



into the compounds (13) or (14) by reaction with elemental fluorine as described hereinbefore.

The groups R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> may be selected from hydrogen, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, perfluoroalkyl, substituted perfluoroalkyl, aryl, substituted aryl or acetoxy. Where any of the groups R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> or R<sub>4</sub> is an alkyl, cycloalkyl or aryl substituent, the said group may include one or more optional, substituents or hetero atoms.

The structures represented by formulae (14) and (16) are cyclic and n may be an integer in the inclusive range from 1 to 8.

In carrying out the reaction, the ratio of fluorine to compound of formula (15) or (16) may be varied within wide limits although it is preferred that the molar ratio is in the range 1.5 to 2.5:1, especially 2.0 to 2.25:1 (fluorine : organic compound).

The ratio of halogen or interhalogen to compound of formula (15) or (16) may be varied between wide limits although it is preferred that the molar ratio is in the range 1.5 to 2.5:1, especially 2.0 to 2.25:1 (halogen/intehalogen : organic compound).

The process according to the present invention therefore additionally provides an inexpensive and convenient synthetic route to difluoromethene containing organic compounds.

Embodiments of the present invention will now be described, by way of example only, with reference to the following Examples:

Example 1: Preparation of 1-(difluorophenylmethyl)-2,4-dimethylbenzene

A solution 2-phenyl-2-(2',4'-dimethylphenyl)-1,3-dithiolane (2.4g, 8.5mmol), iodine (4.3g, 17mmol) and acetonitrile (40ml) was placed in a PTFE fluorination vessel with attached soda lime filled drying tube. Fluorine gas (17mmol) as a 10% mixture in nitrogen was then passed through the stirred solution using narrow bore PTFE tubing at ca 4.0ml/min. The mixture was added to a 10% sodium metabisulfite solution (50ml), extracted with dichloromethane (3x50ml), dried ( $MgSO_4$ ) and evaporated. Column chromatography on silica gel using 9:1 hexane/ether as the eluant gave pure 1-(difluorophenylmethyl)-2,4-dimethylbenzene which was obtained as a clear liquid in 65% isolated yield:  $\delta H$  (250MHz,  $CDCl_3$ ,  $Me_4Si$ ) 2.15ppm (3H, s,  $CH_3$ ), 2.31 (3H, s,  $CH_3$ ), 6.9-7.4 (8H, m, Ar-H);  $\delta F$  (235MHz,  $CDCl_3$ ,  $CFCl_3$ ) -86.7ppm (s);  $m/z$  ( $EI^+$ ) 232 ( $M^+$ , 100%), 217 (24), 211 (21), 197 (33), 154 (89), 127 (27), 105 (16), 77 (15); as compared to the literature data.

Example 2: Preparation of 1-(difluorophenylmethyl)-4-bromobenzene

In a similar reaction to that described in Example 1, 2-phenyl-2-(4' bromophenyl)-1,3-dithiolane gave 1-(difluorophenylmethyl)-4-bromobenzene as a clear liquid in 61% isolated yield:  $\delta H$  (250MHz,  $CDCl_3$ ,  $Me_4Si$ ) 7.32 - 7.52ppm (m, Ar-H);  $\delta F$  (235MHz,  $CDCl_3$ ,  $CFCl_3$ ) -89.5ppm (s);  $\delta C$  (100MHz,  $CDCl_3$ ,  $Me_4Si$ ) 120.37ppm (t,  $^1J$  242,  $CF_2$ ), 124.4 (t,  $^4J$  2.3, C-3"), 125.8 (t,  $^3J$  5.7, C-2"), 127.6 (t,  $^3J$  5.5, C-2'), 128.5 (s, C-4"), 130.1 (t,  $^4J$  1.9, C-3'), 131.7 (s, C-Br), 136.9 (t,  $^2J$  29, C-1"), 137.3 (t,  $^2J$  28.3, C-1');  $m/z$  ( $EI^+$ ) 282 ( $M^+$ , 21%), 284 ( $M^+ + 2$ , 24), 205 (20), 203 (36), 185 (39), 183 (100), 127(35), 105 (42); as compared to the literature data.

9

Example 3: Preparation of 1-(difluoro-4-fluorophenyl-methyl)-4-fluorobenzene

In a similar reaction to that described in Example 1, bis (4'-fluorophenyl)-1,3-dithiolane gave 1-(difluoro-4-fluorophenyl-methyl)-4 fluorobenzene as a clear liquid in 66% isolated yield;  $\delta_H$  (100MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 7.06ppm (4H, m, Ar-H), 7.45 (4H, m, Ar-H);  $\delta_F$  (235MHz, CDCl<sub>3</sub>, CFCl<sub>3</sub>) -86.8 (2F, s, CF<sub>2</sub>), -111.0 (2F, s Ar-F);  $\delta_C$  (100MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 115.62 (d, <sup>2</sup>J 22.0, C-3), 120.20 (t, <sup>1</sup>J 241.8, CF<sub>2</sub>), 128.16 (d t, <sup>3</sup>J 8.4 and 5.5, C-2), 133.63 (t d, <sup>2</sup>J 28.9, <sup>4</sup>J 3.4, C-1), 163.74 (d t, <sup>1</sup>J 250.2, <sup>5</sup>J 2.0, C-4); m/z (EI<sup>+</sup>) 240 (M<sup>+</sup>, 100%), 221 (27), 218 (26), 201 (13), 145 (80), 123 (39), 95 (57); as compared to the literature data.

Example 4: Preparation of difluorodiphenylmethane

In a similar reaction to that described in Example 1, benzothiophenone gave difluorodiphenylmethane as a clear liquid in 56% isolated yield;  $\delta_H$  (250MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 8.43ppm (m, Ar-H);  $\delta_F$  (235MHz, CDCl<sub>3</sub>, CFCl<sub>3</sub>) -89.2ppm (s); m/z (EI<sup>+</sup>) 204 (M<sup>+</sup>, 100%), 183 (37), 127 (89), 77 (23); as compared to the literature data.

Example 5: Preparation of 9,9-difluoro-9H-fluorene

In a similar reaction to that described in Example 1, 9H-fluorenyl-1,3-dithiolane gave 9,9-difluoro-9H-fluorene as a white solid in 52% isolated yield;  $\delta_H$  (250MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 7.35 - 7.7ppm (m, Ar-H);  $\delta_F$  (235MHz, CDCl<sub>3</sub>, CFCl<sub>3</sub>) -112.1ppm;  $\delta_C$  (100MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 120.35ppm (s, Ar-H), 123.22 (t, <sup>1</sup>J 242.6, CF<sub>2</sub>), 123.80 (s, Ar-H), 128.76 (s, Ar-H), 132.00 (s, Ar-H), 138.04 (t, <sup>2</sup>J 25.1, C-1), 139.50 (t, <sup>3</sup>J 5.1, C-2); m/z (EI<sup>+</sup>) 202 (M<sup>+</sup>, 55%), 201 (100), 183 (41), 181 (21), as compared to the literature data.

Example 6: Preparation of 1-(difluorophenylmethyl)-4-chlorobenzene

In a similar reaction to that described in Example 1, 2-phenyl-2-(4'-chlorophenyl)-1,3-dithiolane gave 1-

(difluorophenylmethyl-4-chlorobenzene as a clear liquid in 64% isolated yield;  $\delta_H$  (250MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 7.64 (m, Ar-H);  $\delta_F$  (235MHz, CDCl<sub>3</sub>, CFCl<sub>3</sub>) -89.2ppm (s); m/z (EI<sup>+</sup>) 238 (M<sup>+</sup>, 100%), 240 (M<sup>+</sup> +2, 27), 219 (14), 203 (99), 183 (44), 163 (20), 161 (52), 127 (41), 77 (11), as compared to the literature data.

Example 7: Preparation of  $\beta$ -D-glucopyranosyl fluoride tetraacetate

Elemental fluorine gas (3.4mmol diluted to a 10% solution in nitrogen) was bubbled slowly through a mixture of phenyl-1-thio- $\beta$ -D-glucopyranoside tetraacetate (0.75g, 1.7mmol) and iodine (0.86g, 3.4mmol) in dry acetonitrile (15ml). After the addition of fluorine was complete the solution was poured into 10% sodium metabsulfite and extracted with dichloromethane. The organic layer was washed sequentially with 10% sodium bicarbonate and water, dried (MgSO<sub>4</sub>) and evaporated to a thick yellow syrup. <sup>19</sup>F nmr analysis of the product mixture showed the presence of both anomers with ratio  $\alpha:\beta = 1:6$ . Purification of the product mixture by column chromatography on silica gel with ethyl acetate: petroleum ether (1:1) as eluant yielded pure  $\beta$ -D-glucopyranosyl fluoride tetraacetate (320mg, 54%) as white crystals; m.p. 87-88°C from ether [lit. 89°C];  $[\alpha]_D +20.8$  (lit.,  $[\alpha]_D 20.0$ ); R<sub>F</sub> 0.52; (Found: C, 47.7; H, 5.55. Calc. for C<sub>14</sub>H<sub>19</sub>O<sub>9</sub>F: C, 48.0, H, 5.4%);  $\delta_H$  (400MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.04, 2.05, 2.10, 2.11 (each 3H, s, CH<sub>3</sub> groups), 3.90 (1H, d d d, J<sub>4,5</sub> 9.4, J<sub>5,6a</sub> 4.8, J<sub>5,6b</sub> 2.8, H-5), 4.22 (1H, d d, J<sub>6a,6b</sub> 12.4, J<sub>5,6b</sub> 2.8, H-6b), 4.27 (1H, d d, J<sub>6a,6b</sub> 12.4, J<sub>5,6a</sub> 4.4, H-6a), 5.11 (1H, m, H-2), 5.21 (2H, m, H-3,4), 5.37 (1H, d d, <sup>1</sup>J<sub>H,F</sub> 52.4, J<sub>H1,H2</sub> 5.4, H-1);  $\delta_C$  (100MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 20.6ppm and 20.7 (s, CH<sub>3</sub> groups overlapping), 61.7 (s, C-6), 67.4 (s, C-4), 71.1 (d, <sup>2</sup>J<sub>C,F</sub> 28.6, C-2), 71.8 (d, <sup>3</sup>J<sub>C,F</sub> 8.4, C-3), 72.0 (d, <sup>3</sup>J<sub>C,F</sub> 4.2, C-5), 106.2 (d, <sup>1</sup>J<sub>C,F</sub> 219.7, C-1), 169.1, 169.3, 170.0 and 170.6 (s, C=O groups);  $\delta_F$  (235MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) -141.68ppm (d d, <sup>1</sup>J<sub>H,F</sub> 53.0, <sup>2</sup>J<sub>H,F</sub> 12.5,

## II

F-1); m/z (Cl<sup>+</sup>, NH<sub>3</sub>) 331 (M<sup>+-</sup>F, 100%).

Example 8: Preparation of 4-O-(2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glucopyranosyl)- $\beta$ -D-glucopyranosyl fluoride triacetate

In a similar reaction to that described in Example 7, but using phenyl-4-O-(2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glucopyranosyl)-1-thio- $\beta$ -D-glucopyranoside triacetate as the starting material, <sup>19</sup>F nmr analysis of the crude product mixture obtained showed the presence of both fluoro-anomers with  $\alpha$ : $\beta$  ratio 1:10. Purification of the product mixture by column chromatography on silica gel with ethyl acetate: petroleum ether (7:3) as eluant yielded pure 4-O-(2,3,4,6-tetra-O-acetyl- $\alpha$ -D-glucopyranosyl)- $\beta$ -D-glucopyranosyl fluoride triacetate (375mg, 57%) as white crystals: R<sub>F</sub> 0.62; δ<sub>H</sub> (400MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 2.01, 2.03, 2.05, 2.06, 2.10, 2.11 and 2.12 (each 3H, s, CH<sub>3</sub> groups), 3.99 (1H, m, H-5'), 4.01 (1H, m, H-5), 4.08 (1H, d d, J<sub>H6a',H6b'</sub> 12.4, J<sub>H5',H6a'</sub> 2.4, H-6a'), 4.16 (1H, t, J<sub>H4,H5'</sub> 8.4, H-4), 4.22 (1H, d d, J<sub>H6a,H6b'</sub> 12.0, J<sub>H5,H6b'</sub> 4.4, H-6b), 4.25 (1H, d d, J<sub>H6a',H6b'</sub> 12.8, J<sub>H5,H6b'</sub> 4.0, H-6b'), 4.55 (1H, d d, J<sub>H6a,H6b'</sub> 12.0, J<sub>H5,H6a'</sub> 3.2, H-6a), 4.85 (1H, d d, J<sub>H2',H3'</sub> 10.8, J<sub>H1',H2'</sub> 4.0, H-2'), 4.95 (1H, m, H-2), 5.07 (1H, t, J<sub>H4',H5'</sub> 10.0, H-4'), 5.14 (1H, t, J<sub>H3,H4'</sub> 7.0, H-3), 5.38 (1H, t, J<sub>H3',H4'</sub> 10.0, H-3'), 5.42 (1H, d, J<sub>H1',H2'</sub> 4.0, H-1'), 5.43 (1H, d d, J<sub>H1,F</sub> 52.4, J<sub>H1,H2'</sub> 4.8, H-1); δ<sub>C</sub> (100MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) 20.56, 20.60, 20.62, 20.69, 20.79, 20.86 (each s, CH<sub>3</sub> groups), 61.49 (s, C-6'), 62.64 (s, C-6), 67.98 (s, C-4'), 68.60 (s, C-5'), 69.29 (s, C-3'), 70.15 (s, C-2'), 71.23 (d, <sup>2</sup>J<sub>C,F</sub> 31.6, C-2), 71.97 (s, C-4), 72.29 (s, C-5), 74.02 (d, <sup>3</sup>J<sub>C,F</sub> 5.3, C-3), 95.90 (s, C-1'), 105.46 (d, <sup>1</sup>J<sub>C,F</sub> 219.7, C-1), 169.36, 169.43, 169.98, 170.04, 170.45, 170.55 (each s, C=O groups); δ<sub>F</sub> (376MHz, CDCl<sub>3</sub>, Me<sub>4</sub>Si) -131.9ppm (d d, <sup>1</sup>J<sub>H,F</sub> 52.6, <sup>2</sup>J<sub>H,F</sub> 8.3, F-1); m/z (Cl<sup>+</sup>, NH<sub>3</sub>) 656 (M<sup>+</sup>+18, 52%).

Example 9: Preparation of  $\alpha$ -D-mannopyranosyl fluoride tetraacetate

In a similar reaction to that described in Example 7, but using phenyl-1-thio-D-mannopyranoside tetraacetate as the starting material,  $^{19}\text{F}$  nmr analysis of the product mixture obtained showed the presence of only the  $\alpha$  anomer. Purification of the product mixture by column chromatography on silica gel with ethyl acetate: petroleum ether (1:1) as eluant yielded pure  $\alpha$ -D-mannopyranosyl fluoride tetraacetate (265mg, 47%) as a clear oil;  $R_F$  0.52;  $\delta_H$  (400MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ) 2.1, 2.3, 2.6 and 2.9ppm (each 3H, s,  $\text{CH}_3$  groups), 4.12-4.20 (2H, m, H-5 and H-6a), 4.30 (1H, d d,  $J_{6a,6b}$  12.8,  $J_{5,6b}$  5.2, H-6b), 5.32-5.36 (2H, m, H-3 and H-4), 5.40 (1H, m, H-2), 5.58 (1H, d d,  $J_{H_1,F}$  48.4,  $J_{H_1,H_2}$  2.0, H-1);  $\delta_F$  (235MHz,  $\text{CDCl}_3$ ,  $\text{CFCl}_3$ ) -138.8ppm (d,  $J_{H,F}$  46.4, F-1);  $\delta_C$  (100MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ) 20.54, 20.60 and 20.67ppm (each s,  $\text{CH}_3$  groups), 61.83 (s, C-6), 64.99 (s, C-4), 67.63 (d,  $^2J_{C-F}$  39.3, C-2), 68.13 (s, C-5), 70.85 (d,  $^3J_{C-F}$  3.0, C-3), 104.70 (d,  $^1J_{C-F}$  223.9, C-1), 169.53, 169.62, 169.69 and 170.53 (each s, C=O groups).

Example 10: Preparation of  $\beta$ -D-galactopyranosyl fluoride tetraacetate

In a similar reaction to that described in Example 7, but using phenyl-1-thio- $\beta$ -D-galactopyranoside tetraacetate as the starting material,  $^{19}\text{F}$  nmr analysis of the product mixture obtained showed the presence of only  $\alpha$  and  $\beta$  anomers in ratio  $\alpha:\beta$  1:7. Purification of the product mixture by column chromatography on silica gel with ethyl acetate: petroleum ether (1:1) as eluant yielded pure  $\beta$ -D-galactopyranosyl fluoride tetraacetate (300mg, 51%) as a clear oil;  $R_F$  0.45;  $\delta_H$  (400MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ) 4.06 (1H, t,  $J_{5,6}$  6.4, H-5), 4.21 (2H, d d,  $J_{5,6}$  6.6,  $J_{6a,6b}$  1.6, H-6), 5.05 (1H, d d,  $J_{2,3}$  10.4,  $J_{3,4}$  3.2, H-3), 5.26 (1H, d d,  $J_{H,F}$  54.0,  $J_{1,2}$  7.2, H-1), 5.42 (1H, m, H-4), 5.31 (1H, m, H-2);  $\delta_F$  (235MHz,  $\text{CDCl}_3$ ,  $\text{CFCl}_3$ ) -143.11ppm (d d,  $J_{H,F}$  54.0,  $J_{H,F}$  12.0);  $\delta_C$  (100MHz,  $\text{CDCl}_3$ ,  $\text{Me}_4\text{Si}$ ) 20.53, 20.60 and

13

20.67 ppm (each s, CH<sub>3</sub> groups), 61.29 (s, C-6), 66.37 (s, C-4), 68.75 (d, <sup>2</sup>J<sub>C-F</sub> 24.8, C-2), 69.89 (d, <sup>3</sup>J<sub>C-F</sub> 10.7, C-3), 71.17 (d, <sup>3</sup>J<sub>C-F</sub> 4.5, C-5), 107.08 (d, <sup>1</sup>J<sub>C-F</sub> 218.6, C-1).

Claims

1. A process for the preparation of a selectively fluorinated organic compound, which process includes the reaction of a precursor of the said organic compound, the precursor containing at least one Group VI element selected from sulfur, selenium and tellurium, with a fluorinating agent and another halogenating agent and characterised in that the fluorinating agent is elemental fluorine.
2. A process as in Claim 1 and wherein the Group VI containing precursor is a thiocarbonyl containing substrate.
3. A process as in Claim 1 or Claim 2 and wherein the Group VI containing precursor is contained in an inert solvent.
4. A process as in any one of the preceding claims and wherein the halogenating agent comprises elemental iodine or bromine or an interhalogen compound comprising iodine monochloride or iodine monobromide.
5. A process as in any one of the preceding Claims and wherein the reaction is carried out at a temperature in the range -60°C to +150°C.
6. A process as in any one of the preceding Claims and wherein the fluorine gas is diluted before use by mixing with an inert gas such that the concentration of fluorine in the inert gas is from 1% to 50% by volume.
7. A process for the preparation of fluorine containing molecules of formulae (1), (2), (3), (4) or (5) as hereinbefore defined, comprising converting the corresponding sulfur containing precursor compounds of formulae (6), (7), (8), (9), (10), (11) or (12) as hereinbefore defined, into the compounds (1), (2), (3), (4) or (5) by reaction with elemental fluorine by the process according to any one of the preceding Claims.
8. A process for the preparation of difluorinated compounds of formulae (13) or (14) as hereinbefore

15

defined, comprising converting the corresponding thiocarbonyl compounds of formulae (15) or (16) as hereinbefore defined, into the compounds (13) or (14) by reaction with elemental fluorine by the process according to any one of Claims 1 to 6.

## INTERNATIONAL SEARCH REPORT

International Application No.  
PCT/GB 95/01765

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 6 C07B39/00 C07C17/093

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 6 C07B C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	JOURNAL OF THE CHEMICAL SOCIETY, CHEMICAL COMMUNICATIONS, vol. 2, 1995 LETCHWORTH GB, page 177 R.D. CHAMBERS ET AL. 'The Conversion of Diaryl-1,3-Dithiolanes into gem-Difluoromethylene Compounds by a Combination of Elemental Fluorine and Iodine' see the whole document ---	1-8 -/-

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

30 October 1995

Date of mailing of the international search report

7.11.95

Name and mailing address of the ISA  
European Patent Office, P.O. Box 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+ 31-70) 340-2040, Fax. 31 651 epo nl.  
Fax (+ 31-70) 340-3016

Authorized officer

Bonnevalle, E

## INTERNATIONAL SEARCH REPORT

Intell. Int'l Application No  
PCT/GB 95/01765

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>SYNLETT, no. 3, 1991 STUTTGART DE, pages 191-192, W.B. MOTHERWELL ET AL. 'Observations on the Reaction of Dithioketals with para-Iodotoluene Difluoride: A Novel Route to gem-Difluoro Compounds' see the whole document</p> <p>---</p> <p>JOURNAL OF ORGANIC CHEMISTRY, vol. 51, 1986 EASTON US, pages 3508-3513, S.C. SONDEJ ET AL. 'gem-Difluoro Compounds: A Convenient Preparation from Ketones and Aldehydes by Halogen Fluoride Treatment of 1,3-Dithiolanes' see the whole document</p> <p>---</p>	1,7,8
A		1,7,8
1		